Remarks

Status of the Claims following the Office action mailed June 14, 2006

Claims 1-24 are pending.

Claims 1-24 are rejected.

Amendments to the Claims

Applicants have amended claims 7 and 8 to delete the subscripts in the formulae. The subscripts, which indicated a single occurrence of each component, are uneccessary, and their deletion does not alter the scope of the claims.

Applicants have amended claims 1, 9, and 10 to further clarify that the multimerization domain is a self-multimerization domain, as described throughout the specification (e.g., see the title; the abstract, line 6; page 26, line 4, through page 30, line 2; page 11, line 30; and page 65, line 33 through page 66, line 1.)

The amendments to the claims do not introduce new matter. Applicants request entry of the amendments to the claims into the record.

Rejection of claims 7 and 8 under 35 U.S.C. §112

Claims 7 and 8 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 7 and 8 were rejected for the use of subscripts indicating a single occurrence of each of the elements of a multimeric complex in a chemical formula. Applicants have amended the claims to remove the subscripts, as suggested by Examiner, which renders the rejection moot.

Applicants request reconsideration and withdrawal of the rejection of claims 7 and 8 under 35 U.S.C. 112 in view of the amendments and remarks.

Rejection of claims 1-17 and 24 under 35 U.S.C. §103

Claims 1-17 and 24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Altman et al., 1996, Science 274:94-96 ("Altman") in view of Cormack et al., 1996 Gene 173:33-38 ("Cormack"). Applicants traverse the rejection for the reasons set forth below.

The present rejection is a restatement of the rejection set forth in the Office action dated December 1, 2005. In Applicants' response dated April 3, 2006, Applicants pointed out that the claimed invention is distinguished from the teaching of Altman by at least the elements that mediate multimerization. Altman describes the construction of tetramers of biotinylated MHC-peptide complexes using an intermediate molecule, avidin, that binds up to four biotin molecules. A BirA substrate sequence was incorporated into the MHC-peptide complexes to enable enzymatic biotinylation. Applicants argued, in contrast to the teaching of Altman, multimerization in the present invention is mediated by multimerization domains (i.e., subsequences) within the fusion proteins, such that the fusion proteins self-assemble. Applicants argued that the term "multimerization domain", as used in the specification and claims, does not encompass a BirA substrate sequence, which only facilitates enzymatic biotinylation and does not directly mediate multimerization.

Examiner maintained the rejection on the basis that the term "multimerization domain" could be construed as not limited to self-multimerization domains, but also to encompass a biotinylation domain, such as the BirA substrate sequence, because multiple biotinylated proteins can be bound by avidin to form multimers. Applicants respectfully disagree and maintain that, when read in light of the specification, the term "multimerization domain" does not encompass a BirA substrate sequence. However, in order to expedite prosecution, Applicants have amended the independent claims, claims 1, 9, and 10, to further clarify that the multimerization domain that is a part of the fusion proteins is a self-multimerization domain. Applicants request reconsideration of the rejection in view of the clarifying amendments, for the reasons restated below.

Claim 1

Independent claim 1, as amended, is drawn to a recombinant fusion protein comprising three elements: (1) a GFP-like chromophore; (2) a self-multimerization domain; and (3) an MHC peptide presenting moiety. Applicants submit that the cited prior art, alone or in combination, fails to teach or suggest a recombinant fusion protein comprising these three elements.

Altman describes the construction of tetramers of MHC-peptide complexes based on the binding capacity of avidin, which can bind up to four biotin molecules. Altman made use of the multivalent nature of avid-biotin binding to create tetramers by first binding biotin molecules to MHC-peptide complexes, then using avidin to bind four biotinylated MHC-peptide complexes. The tetrameric complexes were labeled by attaching a fluorophore to the avidin. Altman described the construction of these tetramers as follows:

> To engineer tetrameric peptide-MHC complexes, we first added a 15-amino acid substrate peptide for BirA-dependent biotinylation to the COOH-terminus of the human lymphocyte antigen (HLA)-A2 heavy chain. After folding the heavy-chain fusion protein in vitro in the presence of 2-microglobulin (2M) and a specific peptide ligand, the purified MHC-peptide complex was biotinylated efficiently (70 to 100%) on a single lysine within the BirA substrate peptide (BSP). [...] Tetramers were produced by mixing the biotinylated peptide-MHC complex with phycoerythrin-labeled deglycosylated avidin at a molar ratio of 4:1.

Altman, page 94, column 3 (emphasis added, numeric references removed). As described above, the BirA substrate sequence serves as a substrate for enzymatic biotinylation. However, the presence of a BirA substrate sequence in a protein does not mediate self-multimerization of the protein, and a BirA substrate sequence is not a self-multimerization domain within the recombinant protein. Altman describes the use of a separate multivalent binding moiety (avidin) and an additional biotinylation step to effect multimerization of complexes containing MHC proteins.

Cormack describes the selection of variants of GFP with altered fluorescent properties. The selection involved the creation of a library of GFP-encoding genes containing mutations, expression of the GFP in *E. coli*, and selection of the desired variants using flow cytometry. Cormack suggests that such variant GFP may be used as a marker for gene expression, or as a tag to study protein localization, both applications involving the expression of a GFP-containing fusion protein and the measurement of the intracellular fluorescence. Cormack is silent about the natural multimerization property of some GFP.

The present invention, in contrast to Altman, provides recombinant fusion proteins that multimerize, wherein multimerization is driven and mediated by the self-multimerization domains (i.e., subsequences) of the fusion proteins (specification at page

42, lines 9-10). In other words, the recombinant fusion proteins of claim 1 can self-assemble, mediated by subsequences of the proteins. Altman fails to teach or suggest that the natural multimerizing property of a protein such as a GFP could be used to create multimers of MHC proteins, and in particular, fails to teach or suggest a recombinant protein comprising the combination of an MHC peptide-presenting moiety and a self-multimerization domain.

Cormack, which is silent about the natural multimerization property of some GFP, fails to teach or suggest that the natural multimerizing property of some GFP could be used to create multimers of MHC, and fails to make up for the lack of teaching in Altman. For at least this reason, the teachings of Altman and Cormack, alone or in combination, fail to teach or suggest the invention of claim 1, and the rejection should be withdrawn.

Claims 2-8, 11-17, and 24

Claims 2-8, 11-17, and 24 depend from claim 1. As discussed above, Altman and Cormack, alone or in combination, fail to teach or suggest the invention of claim 1. As claims that depend from a novel and non-obvious base claim are likewise novel and non-obvious, Altman and Cormack, alone or in combination, fail to teach or suggest claims 2-8, 11-17, and 24. For at least this reason, the rejection of claims 2-8, 11-17, and 24 should be withdrawn.

Claims 9 and 10

Claims 9 and 10 are independent claims essentially corresponding to claim 1 (recombinant fusion protein) and claim 6 (multimeric protein complex), respectively, but written in means plus function form. As with claim 1, Applicant have amended claims 9 and 10 to recite a means for self-multimerization. Altman and Cormack, alone or in combination, fail to teach or suggest claims 9 and 10 for the reasons set forth above regarding claim 1 and dependent claim 6. For at least this reason, the rejection of claims 9 and 10 should be withdrawn.

In summary, the cited prior art, alone or in combination, fails to teach or suggest the combination of elements recited in the claims, and, for at least this reason, the rejection of claims 1-17 and 24 should be withdrawn. Applicants request reconsideration

and withdrawal of the rejection of claims 1-17 and 24 under 35 U.S.C. §103(a) in view of the above amendments and remarks.

Rejection of claims 18-22 under 35 U.S.C. §103

Claims 18-22 were rejected under 35 U.S.C. §103(a) as being unpatentable over Altman et al., 1996, Science 274:94-96 ("Altman") in view of Cormack et al., 1996 Gene 173:33-38, and further in view of U.S. Patent No. 6,232,445 ("the '445 patent"). Applicants traverse the rejection for the reasons set forth below.

Claims 18-22 are drawn to kits containing the multimeric protein complex of claim 7, which depends from claim 1 (now amended). Examiner cited the '445 patent as teaching that recombinant MHC molecules can be incorporated into a kit. However, the '445 patent fails to make up for the lack of teaching in the combination of Altman and Cormack to make the multimeric protein complex of claim 7. Thus, the teachings of Altman, Cormack, and the '445 patent, alone or in combination, fail to teach or suggest kits that contain the multimeric protein complex of claim 7. For at least this reason, the rejection of claims 18-22 should be withdrawn.

Applicants request reconsideration and withdrawal of the rejection of claims 18-22 under 35 U.S.C. §103(a) in view of the above amendments and remarks.

Rejection of claim 23 under 35 U.S.C. §103

Claim 23 was rejected under 35 U.S.C. §103(a) as being unpatentable over Altman et al., 1996, Science 274:94-96 ("Altman") in view of Cormack et al., 1996 Gene 173:33-38, and U.S. Patent No. 6,232,445 ("the '445 patent"), and further in view of U.S. Patent No. 4,902,613 ("the '613 patent"). Applicants traverse the rejection for the reasons set forth below.

Claim 23 is drawn to a kit of claim 18 or 21, both of which are drawn to kits containing the multimeric protein complex of claim 7, which depends from claim 1 (now amended), with the additional element of a red blood cell lysing agent. Examiner cited the '613 patent as teaching a red blood cell lysing agent.

As discussed above, the teachings of Altman, Cormack, and the '445 patent, alone or in combination, fail to teach or suggest the kits of claim 18 or 21, which contain the

multimeric protein complex of claim 7. Claim 23 merely recites the inclusion of an additional component to the kits of claims 18 or 21, which both are novel and non-obvious over the cited prior art. The teaching of the '613 patent of a lysing agent fails to make up for the lack of teaching in the combination of Altman, Cormack, and the '445 patent to make the kits of claims 18 or 21, and, thus, the combination of Altman, Cormack, the '445, and the '613 patent fails to teach or suggest such kits with the additional element of a red blood cell lysing agent. For at least this reason, the rejection should be withdrawn.

Applicants request reconsideration and withdrawal of the rejection of claim 23 under 35 U.S.C. §103(a) in view of the above amendments and remarks.

Conclusion

Applicants believe that all rejections applied to the claims have been overcome and that the present application is now in condition for allowance.

Respectfully submitted,

8/8/06
Date

Douglas A. Petry, Ph.D.
Reg. No. 35,321
Agent for Applicants
Customer No. 26253
Tel: (408) 518-5074
Fax: (408) 432-6493